# INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference RE/PG4939A	FOR FURTHER ACTION  See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)										
International application No. PCT/GB 03/03721	International filing date (day/montal 28.08.2003	th/year) Priority date (day/month/year) 30.08.2002									
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International Patent Classification (IPC) or be A61 K39/00	om nauonai ciassilicauon and ir C										
Applicant GLAXO GROUP LIMITED et al.	g agreed described as the	الراع . المراجع المراج									
This international preliminary example Authority and is transmitted to the second control of the second c	mination report has been prepa applicant according to Article 3	red by this International Preliminary Examining 36.									
2. This REPORT consists of a total	of 8 sheets, including this cove	r sheet.									
hoon amended and are the	nied by ANNEXES, i.e. sheets basis for this report and/or shee n 607 of the Administrative Inst	of the description, claims and/or drawings which have ts containing rectifications made before this Authority ructions under the PCT).									
These annexes consist of a total	of 32 sheets.										
3: This report contains indications re	elating to the following items:	V = 10 MeV 10 MeV									
I ⊠ Basis of the opinion		f									
II Priority											
	·	inventive step and industrial applicability									
IV  Lack of unity of inven		and the annual to invention atom or industrial applicability									
V 🖾 Reasoned statement citations and explana	under Rule 66.2(a)(ii) with rega tions supporting such statemen	rd to novelty, inventive step or industrial applicability; t									
VI 🗆 Certain documents ci											
	international application										
VIII   Certain observations	on the international application	· ·									
Date of submission of the demand	Date	of completion of this report									
04.03.2004	24.1	1,2004									
Name and mailing address of the internation preliminary examining authority:	nal Autho	rized Officer									
European Patent Office D-80298 Munich		ero, M									
Tel. +49 89 2399 - 0 Tx: 523 Fax: +49 89 2399 - 4465		hone No. +49 89 2399-8542									

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/GB 03/03721

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**Description, Pages** 

1. With regard to the **elements** of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	1-6,	9-17, 19-32	as originally filed
	7, 8,		received on 25.11.2003 with letter of 24.11.2003
	1-14,2		प्रदेशमान् । प्राप्तास्थान् । प्रदेशमान् । प्रदेशमान् । प्रदेशमान् । प्रदेशमान् । प्रदेशमान् । प्रदेशमान् । प्
	Seq	uence listings part of t	
	1-24		received on 15.12.2003 with letter of 12.12.2003
	Clai	ms, Numbers	
	1-7		as originally filed
	Drav	wings, Sheets	
		-3/11, 5/11, 9/11, 10/11	as originally filed
		, 6/11, 7/11, 8/11, 11/11	received on 25.11.2003 with letter of 24.11.2003
2.	With lang	regard to the <b>language</b> uage in which the intern	e, all the elements marked above were available or furnished to this Authority in the ational application was filed, unless otherwise indicated under this item.
	The	se elements were availa	ble or furnished to this Authority in the following language:, which is:
		the language of a trans	lation furnished for the purposes of the international search (under Rule 23.1(b)).
		the language of publica	tion of the international application (under Rule 48.3(b)).
		the language of a trans Rule 55.2 and/or 55.3).	lation furnished for the purposes of international preliminary examination (under
3.	Witl inte	n regard to any <b>nucleot</b> i rnational preliminary exa	de and/or amino acid sequence disclosed in the international application, the amination was carried out on the basis of the sequence listing:
		contained in the interna	ational application in written form.
		filed together with the in	nternational application in computer readable form.
	$\boxtimes$		to this Authority in written form.
	×	furnished subsequently	to this Authority in computer readable form.
	⊠	in the international app	subsequently furnished written sequence listing does not go beyond the disclosure lication as filed has been furnished.
	$\boxtimes$	The statement that the listing has been furnish	information recorded in computer readable form is identical to the written sequence led.
4.	The		ulted in the cancellation of:
		the description, pa	ages:
·			

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/GB 03/03721

		the claims,	Nos.:						
		the drawings,	sheets:						
5.		This report has been been considered to g	n establishe go beyond	ed as i	if (some of) tl sclosure as f	ne amendment iled (Rule 70.2)	s had not bee (c)).	n made, since th	ney have
		(Any replacement sh report.)	neet contail	ning s	uch amendm	ents must be r	eferred to und	der item 1 and ar	nexed to this
6.	Add	litional observations,	if necessar	у:					
	see	separate sheet							
	er a	ment of the second			. • •	N - 1 :	4 1 - 1 - 1 - 1	• •	
۷.	Rea cita	asoned statement ur tions and explanation	nder Articl ons suppo	e 35(2 orting	2) with regar such staten	d to novelty, i nent	nventive ste	p or industrial a	ıpplicability;
1.	Stat	tement							
	Nov	velty (N)		Yes: No:	Claims Claims	1-7			
	Inve	entive step (IS)	•	Yes:	Claims				
		5vo 0.0p (.0)		No:	Claims	1-7			
	Indi	ustrial applicability (IA	•	Yes: No:	Claims Claims	1-7			
2.	Cita	ations and explanation	ns						
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#### **SECTION I**

**Additional observations** 6.

.. .. . . .

- 6.1 Sequence listing pages 1-24 filed with the letter of 12.12.03 do not form part of the application (Rule 13ter.1(f) PCT).
- 6.2 The amendments to the description and figures submitted with the Applicants' letter of 24.11.03 do not appear to contravene Art. 34(2)(b) PCT.

#### **SECTION V**

CITATIONS AND EXPLANATIONS 2.

graphs a market .

- 2.1 In view of the priority documents pertaining to the present application, the international patent application WO 02/070711 (publication date 12.09.02; filing date 01.03.02) cited in the International Search Report under the "P" category, is not to be regarded as state of the art according to Rule 64 (1) PCT, as the date of priority of 30.08.02 is validly claimed for the corresponding relevant parts of the present disclosure. This document (a co-pending patent application also referred to in the present description) is nevertheless brought to the Applicant's attention inview of the provisions of Article 54(3)(4) EPC.
- 2.2 The following documents have been considered for the purposes of this report:

D1: WO 00/65058 (also cited in the application)

D2: WO 01/62287 (also cited in the application)

D3: WO 01/34645

D4: WO 02/32450

2.3 Novelty and inventive step (Art. 33(2) and (3) PCT)

Having regard to the documents cited in the International Search Report the subject-matter hereby claimed (cf Claims 1-7) is considered to meet the novelty requirements of Art. 33(2) PCT, since a vaccine composition comprising the same components which should be contained in the hereby claimed vaccine

compositions appears not to be disclosed in the available prior art.

Nevertheless, the application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter claimed does not involve an inventive step (Rule 65(1)(2) PCT).

The technical problem underlying the present application may be regarded as the provision of an improved therapy for the treatment of diseases that are treatable with neutralization of interleukin 13 (IL-13), such as chronic obstructive pulmonary disease (COPD), asthma or atopic disorders such as atopic dermatitis or allergic rhinitis.

The present solution to the problem posed basically relies on autovaccine compositions based on modified autologous IL-13, capable of breaking the tolerance to self IL-13 antigen, which compositions comprise as adjuvant an immunostimulatory oligonucleotide containing at least one unmethylated CG motif and a saponin.

The hereby claimed solution appears not to involve an inventive step for the following reasons:

As outlined in the description (cf page 3, third paragraph) the state of the art provides evidence of the relevant role played by the Th2-type cytokine IL-13 in ... different pathological conditions, for instance, in the development of allergenic asthma (see also D2, page 4, lines 9-26 and the passage on page 2, lines 3-11 of D3).

The related prior art (e.g. D1 and D2) also reveals that the Th2-type cytokine IL-5 plays a prominent role in inflammatory responses accompanying conditions as. asthma and other chronic allergic diseases.

In line with the above findings, both IL-5 and IL-13 molecules have been proposed in D2 as possible antigenic components for use in asthma or allergy vaccines, aimed at neutralisation of said cytokines (see e.g. Claim 7).

**EXAMINATION REPORT - SEPARATE SHEET** 

Moreover, D1 discloses a vaccine for the treatment of asthma, or other chronic allergic conditions, based on IL-5 analogues which are able to induce antibodies against self-IL-5. As noted in the paragraph bridging pages 4-5 of the present application, one of the types of modified IL-5 analogues employed for the vaccination purposes of D1 is an IL-5 immunogen, which has been supplemented with foreign T-cell epitopes whilst maintaining the IL-5 B cell epitopes. The methods employed to prepare said immunogenic IL-5 analogues, capable of breaking self-tolerance to autologous IL-5, are well established in the related technical field (see for instance the observations on page 4, 4th paragraph of the present application).

In view of the above, a skilled artisan facing the problem of providing an improved therapy for the treatment of asthma, devoid of the drawbacks associated with the current treatments mentioned on page 5, 2nd paragraph of the present disclosure, or alternative to the methods disclosed in D3 (see e.g. Claims 4 and 6), would be motivated to apply the teachings of D1 with equivalent effect to prepare an autologous vaccine based on IL-13.

On the other hand, for the vaccination purposes hereby pursued, the use of an adjuvant comprising a combination of a saponin and a immunostimulatory oligonucleotide containing at least one unmethylated CG motif merely represent one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. It is noted that at the date of priority of the present application the desirable properties of adjuvant compositions comprising oligonucleotides containing CpG motifs (e.g. the hereby referred to as OLIGO 4) and a saponin such as QS21 were well known, e.g. from D4, to the person skilled in the art (see also page 22, first paragraph of the present description).

Hence, no inventive merit is a priori recognisable in claiming the hereby proposed vaccine compositions (cf present Claims 1-7).

Furthermore, the experimental data provided in the present application (cf Examples 1 and 2 on pages 27-31) do not substantiate that a solution to the problem posed has been achieved. Example 1 relates to the preparation of a chimeric IL-13 molecule combining the sequence of predicted antigenic loops

derived from murine IL-13 with the sequence of predicted structural regions taken

**EXAMINATION REPORT - SEPARATE SHEET** 

from human IL-13. In Example 2 the required potency of an IL-13 autovaccine for treatment of asthma (in mice) is estimated by determining the level of mouse IL-13 neutralization required to overcome the "ovalbumin challenge" in the mouse asthma model, based on passive administration of rabbit anti-mouse IL-13 antibody (emphasis added). Finally, the "Vaccination studies" referred to in Example 3 only constitute an invitation to carry out pertinent tests whose results could eventually validate any inventive contribution associated with the hereby proposed therapeutic approach.

Accordingly the application as originally filed contains no suitable technical information which could substantiate the presence of any unexpected therapeutic result in connection, for instance, with the proposed methods of treatment described on page 22, last paragraph bridging over pages 23-24. These passages therefore appear to be of a mere predictive nature devoid of inventive merit vis-àvis the teachings of the related prior art discussed above.

#### 2.4 Further comments

- For the reasons outlined in the two last paragraphs of item 2.3 above, present (i) Claims 1-7 are not (technically) supported by the description as required by Art. 6 PCT.
- (ii) Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. By merely referring to "an immunogen that is capable of generating an immune response in a vaccinee against self IL-13" the claim attempts to define the compositions of interest in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

The above deficiency (Art. 6 PCT) affects mutatis mutandis the subject-matter encompassed by Claims 2, 5 and 6 dependent thereon.

- The intended vaccine composition according to instant Claim 7 appears to be redundant with the vaccine composition presently defined in Claim 4, contrary to the conciseness requirements of Art. 6 PCT.
- (iv) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

**EXAMINATION REPORT - SEPARATE SHEET** 

disclosed in the documents D3 and D4 is not mentioned in the description, nor are these documents identified therein.



situation (that is to say for use in vaccination of a human with a human protein sequence as the immunogen).

In one such embodiment of the present invention, the immunogens comprise a chimaeric IL-13 sequence that comprises substitution mutations to swap one or more of the human sequence amino acids with the equivalent amino acids found in the same positions within the sequence of IL-13 from another mammalian species. In the context of a human vaccine immunogen, the object of the chimaeric sequences is to maximise the amino acid sequence diversity between the immunogen and human native IL-13, whilst keeping maximal shape and conformational homology between the two compositions. The chimaeric immunogen achieves this by substituting amino acids found in regions predicted to be masked from the surface. Most preferably the amino acids are substituted with amino acids that are found in equivalent positions within an IL-13 sequence from another mammalian species. In this way, sequence diversity is achieved with minimal alteration to the overall shape/configuration of the immunogen.

In one aspect of the present invention, the human IL-13 immunogen comprises substitution mutations in areas that are associated with alpha helical regions, which substitutions involve swapping the human amino acid with the amino acid that appears in the same position within the IL-13 sequence of a different mammalian species.

Most preferably, there are substitution mutations in a plurality of sites within the IL-13 sequence, wherein at least two or more of the mutation sites comprise a substitution involving amino acids taken from different non-human mammalian species, more preferably the substitutions involve amino acids taken from 3 or more different non-human mammalian species, and most preferably the substitutions involve amino acids taken from 4 or more different non-human mammalian species.

Preferably, the substitutions in the human IL-13 sequence do not occur in at least six of the areas of high interspecies conservation: 3PVP, 12ELIEEL, 19NITQ, 28LCN, 32SMVWS, 50SL, 60AI, 64TQ, 87DTKIEVA, 99LL, 106LF.

The preferred IL-13 element of the vaccines of the present invention are human chimaeric IL-13 sequences which have a similar conformational shape to native human IL-13 whilst having sufficient amino acid sequence diversity to enhance its

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immunogenicity when administered to a human, characterised in that the chimaeric IL-13 immunogen has the sequence of human IL-13 comprising:

- (a) substitution mutations in at least two of the following alpha helical regions:
  PSTALRELIEELVNIT (SEQ ID NO. 24), MYCAALESLI (SEQ ID NO. 25),
  KTQRMLSGF (SEQ ID NO. 26) or AQFVKDLLLHLKKLFRE (SEQ ID NO. 27),
  (b) comprises in unmutated form at least six of the following regions of high inter-species conservation 3PVP, 12ELIEEL, 19NITQ, 28LCN, 32SMVWS, 50SL, 60AI, 64TQ, 87DTKIEVA, 99LL, 106LF, and
- (c) optionally comprises a mutation in any of the remaining amino acids, wherein any substitution performed in steps a, b or c is a structurally conservative substitution.

The numerical prefix to the amino acids listed, refers to the positional number of the amino acid sequence in the mature form of human IL-13, wherein the first residue "G" is assigned the number 2.

In the context of step (a) of the above chimaeric IL-13 element, preferably at least two, more preferably at least three and most preferably all four alpha helical regions comprise at least one substitution mutation. In the context of step (b) preferably at least 7, more preferably at least 8, more preferably at least 9, more preferably at least 10, and most preferably all 11 of the regions are unmutated.

Preferably greater than 50% of these substitutions or mutations in the above chimaeric IL-13 element, comprise amino acids taken from equivalent positions within the IL-13 sequence of a non-human. More preferably more than 60, or 70, or 80 percent of the substitutions comprise amino acids taken from equivalent positions within the IL-13 sequence of a non-human mammal. Most preferably, each substitution or mutation comprise amino acids taken from equivalent positions within the IL-13 sequence of a non-human mammal.

Again in the context of the chimaeric human IL-13 element, preferably greater than 50% of these substitutions or mutations occur in regions of human IL-13 which are predicted to be alpha helical in configuration. More preferably more than 60, or 70, or 80 percent of the substitutions or mutations occur in regions of human IL-13 which are predicted to be alpha helical in configuration. Most preferably, each substitution or

preferred that the signal sequence is a non-human derived sequence that comprises a T-cell epitope, to further provide T-cell help. None of the disclosed preferred sequences have a stop codon as it may be useful to express them fused to other molecules eg immunoglobulin Fc, 6His to facilitate production or purification.

The numbering system used herein conforms with normal practice in the field of IL-13, in that the G in "GPVPP" is referred to as residue 2, and the remaining amino acids are numbered accordingly.

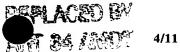
In one aspect of the present invention there is provided a method for the manufacture of a human chimaeric IL-13 vaccine comprising the following steps:

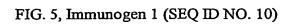
(a) taking the sequence of human IL-13 and performing at least one substitution mutation in at least two of the following alpha helical regions: PSTALRELIEELVNIT, MYCAALESLI, KTQRMLSGF or AQFVKDLLLHLKKLFRE,

- (b) preserving at least six of the following regions of high inter-species conservation 3PVP, 12ELIEEL, 19NITQ, 28LCN, 32SMVWS, 50SL, 60AI, 64TQ, 87DTKIEVA, 99LL, 106LF,
- (c) optionally mutating any of the remaining amino acids,
- (d) attaching a source of T-cell epitopes that are foreign with respect to any human self epitope and also foreign with respect to any mammalian IL-13 sequence, to form an IL-13 immunogen, and
- (e) combining the IL-13 immunogen with an adjuvant composition comprising a saponin and an immunostimulatory oligonucleotide comprising at least one unmethylated CG dinucleotide,

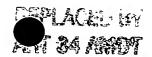
characterised in that any substitution performed in steps a, b or c is a structurally conservative substitution.

In the context of step (a) preferably at least two, more preferably at least three and most preferably all four alpha helical regions comprise at least one substitution mutation. In the context of step (b) preferably at least 7, more preferably at least 8, more preferably at least 9, more preferably at least 10, and most preferably all 11 of the regions are unmutated.





5		GGCCCTGTGCCTCCTTAGCGCCCTCAAGGAGCTCATTGAGGAGCTGGCCAACATCACC	
	1	CCGGGACACGGAGGAGATCGCGGGAGTTCCTCGAGTAACTCCTCGACCGGTTGTAGTGG	С
10		G P V P P S S A L K E L I E E L A N I T	
10		CAGAACCAGAAGGCTCCGCTCTGCAATGGCAGCATGGTATGGAGCATCAACCTGACAGCT	20
	61	GTCTTGGTCTTCCGAGGCGAGACGTTACCGTCGTACCATACCTCGTAGTTGGACTGTCGA	20
15		Q N Q K A P L C N G S M V W S I N L T A	
	121	GGCATGTACTGTGCAGCCCTGGACTCCCTGATCAACGTGTCAGGCTGCAGTGCCATCGAG	во
20		CCGTACATGACACGTCGGGACCTGAGGGACTAGTTGCACAGTCCGACGTCACGGTAGCTC G M Y C A A L D S L I N V S G C S A I E	
	181	CGGACCCAGAGGATCTTGAGCGCCTTCTGCCCGCACAAGGTCTCAGCTGGGCAGTTTTCC	40
	101	GCCTGGGTCTCCTAGAACTCGCGGAAGACGGGCGTGTTCCAGAGTCGACCCGTCAAAAGG	ŧU
25		RTQRILSAFCPHKVSAGQFS	
	241		00
		TCGAACGCACAGGCTCTGTGGTTTTAGCTCCACCGGGTCAAACATTGCCTGGACGAGCAT S L R V R D T K I E V A Q F V T D L L V	
30		CATTTAAAGAGACTTTTTCGCCAGGGAACGTTCAAC	
	301	GTAAATTTCTCTGAAAAAGCGGTCCCTTGCAAGTTG	
35		H L K R L F R Q G T F N	



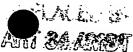
### FIG 11, Immunogen 7 (SEQ ID NO. 16)

5														-						TTGG
				•							•			•			•			W
10																				.CGGC
					S															-
15										-		-	_							TGAT
	N	W	Y	W	F	D	N	s	G	E	M	A	T	G	W	K	K	Ι	A	D
																				GGAC
20	K	W	Y	Y	F	N	E	E	G	A	M	K	T	G	W	v	K	Y	K	D
	AC																			TAAG
25	T				L															
																				.CGGA
	F	I	G	I	T	E	G	v	M	v	s	N	A	F	I	Q	s	A	D	G
30																				TGTG
	T	G	W	Y	Y	L	K	P	D	G	T	L	A	D	R	P	E	G	P	v
35					CGC															CCAG
	P	P	s	s	A	ŗ	ĸ	E	L	I	E	E	L	A	N	I	T	Q	N	Q
																				GTAC
40					С									-						-
	TG																			CCAG
45	С				D															
																				GCGT
																				R
50																				AAAG
	V	R	D	T	K	I	E	v	A	Q	F	V	T	D	L	ь	V	Н	L	K
55	AG	ACT	TTT	TCG -+-	CCA	.GGG	AAC	GTT 	CAA	С -										
	R	L	F	R	Q	G	т	F	N											



### FIG. 12, Immunogen 8 (SEQ ID NO. 17)

5	TO	CTC	TC	TTC	TTC	TAF	CAT	GGC	:GAA	CAC	CCA	GAT	GAA	GTC	CGA	TAA	TAA.	CAT	CAT	cccc
	s	s	н	s	s	N	М	A	N	Т	Q	М	ĸ	s	D	ĸ	I	I	I	A
10	CACAGGGGAGCTAGCGGGTATCTGCCTGAGCACACCCTGGAGTCCAAGGCTCTGGCGTTC															GTTC				
10				Α			Y		р	Е	H	T	L	E	s			L	A	F
	GC	CCA	\GC#	\GGC	TGA	CTA	CCI	'GGA	.GCA	.GGA	CCI	'GGC	GAI	GAC	'AAA'	GGA	TGC	ССС	CCI	CGTG
15	A	Q	Q	Α	D	Y	L	E	Q	D	L	A	М	T	к	D	G	R	L	v
	G7	GAT	CCZ	TGA	CCA	TTI	TCI	CGA	CGG	ACT	GAC	:CGA	CGI	'CGC	CAA	GAA	GTI	ccc	CCA	CCGC
20	v	I	н	D	н	F	L	D	G	L	T	D	v	A	к	к	F	P	н	R
20	CZ	TAC	GAZ	\GGA	CGG	GAG	GTA	TTA	CGI	'GAT	TGA	CTT	'CAC	CCI	CAA	GGA	GAT	CCA	GAG	CCTG
	н	R	к	D	G	R	Y	Y	v	I	D	F	T	ь Г	к	Е	I	Q	s	L
25	G#	GAT	GAC	CGA	GAA	CTI	CGA	GAC	:CGG	CCC	TGT	'GCC	TCC	CTC	TAG	CGC	CCI	CAA	GGA	GCTC
	E	М	Т	E	N	F	E	T	G	P	v	P	P	s	s	A	r+	ĸ	E	L
30	ΑT																			CATG
20	I	E	Е	L	A	N	I		Q		•			•			•		s	M
	GI	ATG	GAG	CAT	CAA	CCI	GAC	AGC	TGG	CAT	'GTA	.CTG	TGC	AGC	CCI	'GGA	CTC	CCI	GAT	CAAC
35	v	W	s	I	N	ь	T	A	Ġ	М	Y	С	A	-+- A	L	D	s	L	I	N
	GI	GTC	AGC	CTG	CAG	TGC	CAT	CGA	.GCG	GAC	CCA	GAG	GAT	CTT	GAG	CGC	CTT	CTG	ccc	GCAC
40	v	s	G	C	s	A	I	E	R	Т	Q	R	I	L L	s	A	F	С	P	н
40	AA	GGT	CTC	AGC	TGG	GCA	GTT	TTC	CAG	CTT	GCG									GGCC
	к	v	s	A	G	Q	F	s	s	ь	R			D		К	I		v	•
45	CA	GTT	TGI	'AAC	GGA	CCT	GCT	CGT	ACA	TTT	AAA	GAG	ACT	TTT	TCG	CCA	.GGG	AAC	GTT	CAAC
	Q	F	v	T	D	L	L	v	Н	L	к	R	L	F	R	Q	G	T	F	N

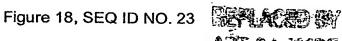


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#### FIG. 13, Immunogen 9 (SEQ ID NO. 18)

5																				
	TT	TAA'	TAA'	TTT	TAC	CGT	TAG	CTT"	rtg	GTT	GCG	TGT	TCC	TAA	AGT.	ATC	TGC	TAG	TCA'	TTTA
	F	N	N	-+- F	т	v	s	F	W	ь 	+ R	v	P	-+- K	v	s	+ A		Н	+ L
10	GA	AGG																		CATC
	E	G	P	•	P	P	•				•		ь	•		E	•			I
15	AC	CCA	GAA	CCA	GAA	GGC	TCC	3CT	CTG	CAA	TGG	CAG	CAT	GGT.	ATG	GAG	CAT	CAA	CCT	GACA
	T	Q	N	Q	K	A	P	L	С	N	Ğ	s	M	v	W	s	ı.	N	L	T
	GC'												CAA		GTC	AGG	CTG	CAG'	TGC	CATC
20	A	G	M	Y	С	A	A	L	D	s	L	I	N	v	s	G	c	s	A	I
		GCG											GCA		GGT		AGC	rgg	GCA	GTTT
25	E.	R	T	Q	R	I	L	s	A	F	C	P	H	ĸ	v	s	A	G	Q	F
	TC	CAG	CTT(	GCGʻ	TGT	CCG	AGA(	CAC	CAA	TAA	CGA	GGT	GGC	CCA	GTT	rgt:	AAC	GGA(	CCT	GCTC
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